PATENT
Attorney Docket No.: ST94014-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Laurent PRADIER *et al.*

Appl. No.: 08/716,209

Filed: October 9, 1996

For: RECOMBINANT ADENOVIRUS CODING FOR BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF)

Art Unit: 1647

Examiner: S. Gucker

Assistant Commissioner for Patents
Washington DC 20231

Reply to Request for Information (Paper No. 38)

In reply to the Office Communication dated September 23, 2002 (Paper No. 38), applicants submit the following answers to the information request. Applicants submit that this is a complete and/or good faith effort to completely reply to the request for information. Furthermore, applicants submit that this request for information is unnecessary and request that it be withdrawn. Applicants have previously submitted reasons why the request is unnecessary but have not received a response from the Patent Office.

REQUEST FOR EXTENSION OF TIME

As permitted under 37 C.F.R.§ 1.136(a) and specifically allowed in Paper No. 38, Applicants request a four-month extension of time to respond to the Communication mailed September 23, 2002 (Paper No. 38). Accordingly, the time for response is extended up to and including February 23, 2003. A payment form covering the required extension of time fee is enclosed. In the event that any variance exists between the amount enclosed and the fees required by the U.S. Patent and Trademark Office, please charge or credit the variance to the undersigned's Deposit Account No. 50-1129. The Commissioner is hereby authorized to charge any fee required to keep this application pending and not accounted for, including the extension of time fee, to Deposit Account No. 50-1129.

RESPONSE TO COMMUNICATION

The Examiner asserted that the response filed May 23, 2002, was not fully responsive. Applicants disagree. However, to avoid abandonment, applicants submit the following in response to the Examiner's questions regarding the adenovirus discussed in the *Science* publication.

Applicants respectfully note that the format in which the requests from the Examiner were presented in Paper No. 38 was not specific or straightforward requests. Information was requested in the statement "No attempt was made to state on the record whether the E2, E4, or L1-L4 genes were nonfunctional, whether the adenovirus comprised an ITR and a sequence permitting encapsulation, or whether the adenovirus was type Ad 2 or Ad 5" (*see* Paper No. 38). The only adenovirus the Examiner could be referring to is the Ad.RSVbgal vector of Le Gal La Salle (*Science* 259:988-990). This is the vector discussed in the paper and the vector previously discussed in the response filed May 23, 2002.

Applicants' response addresses each of the specific topics where, allegedly, no attempt was made to state information on the record. Applicants also enclose a detailed response discussing the origin of the Ad.RSVbgal vector sequences, their availability, and the Ad gene deletions contained in that vector.

A representative of the assignee asked a co-author of the *Science* publication the following questions, and the answers, translated answers, and additional comments appear after each.

Request: The Examiner asks whether the E2, E4, or L1-L5 genes were nonfunctional [in the adenovirus of Le Gal La Salle *Science* paper].

Answer: The virus used in Le Gal La Salle's article (Science, 259: 988-990, 1993) had the E1 and E3 genes deleted. LacZ was inserted into the E1 region. The E3 deletion originated from the Ad5 recombinant adenoviruses of Thimmappaya et al. (Cell vol. 31, p. 543, 1982, copy enclosed). More specifically, the Ad.RSVbgal adenovirus is derived from Ad dl327, which is derived from the dl324 specifically noted in Thimmappaya, and thus these two viruses carry the same E3 deletion. The only difference between Ad dl327 and Ad dl324 is that Ad dl327 is not deleted for E1 whereas Ad dl324 is. To my knowledge, the construction of Ad dl327 has not

been reported in the literature. This is the reason why we refer to the paper of Thimmappaya to describe our Ad.RSVbgal vector.

The E3 deletion noted in Thimmappaya corresponds to the 28591-30474 XbaI fragment of Ad5 (see page 549 of Thimmappaya, first column under "Plasmids, Viruses, Cells and Enzymes"), which is the fragment deleted in the Ad.RSVbgal vector of Le Gal La Salle. The E2, E4 and L1-L5 genes were not deleted in the virus used in Le Gal La Salle's article.

Thimmappaya notes that the E1 and E3 deleted adenoviral vectors "grow normally on 293 cells, which contain and express the early region 1 segment that they lack" (see page 549, top of second column). The same is true of the E1 and E3 deleted adenovirus vectors of Le Gal La Salle. This indicates that with the E1 region complemented by the 293 cells, the adenoviruses contain functional genes for normal viral growth. Accordingly, the E2, E4 and L1-L5 genes are functional in the adenovirus vectors of Le Gal La Salle. In the absence of E1 or the complementation by 293 cells, however, the transcription of these genes is strongly inhibited.

Applicants also note the specification at page 9, where the applicants discuss the defective recombinant adenoviruses contain non-functional E1 gene and at least one of E2, E4, and L1-L5 genes in the particularly preferred embodiment of the invention (page 9, lines 18-19). The adenoviral vectors of Le Gal La Salle differ when comparing the same set of genes because of at least the fact that the vectors of Le Gal La Salle possess only a deleted or non-functional E1 gene.

Request: The Examiner asks whether the adenovirus [of Le Gal La Salle] contained an ITR.
Answer: The adenovirus contained one ITR on each extremity.

Request: The Examiner asks whether the adenovirus [of Le Gal La Salle] contained a sequence permitting encapsulation.
Answer: The virus contained a sequence permitting encapsulation.

Request: The Examiner asks whether the adenovirus [of Le Gal La Salle] was type Ad 2 or Ad 5.
Answer: The virus was Ad5.

Applicants believe that the requests listed above constitute the only information requested from them. These requests have been restated from Paper No. 38 for clarity and completeness. If the Examiner was asking for additional information that is not represented by the above requests, please call the undersigned to clarify. Applicants have made a good faith reply to the request for information. In conjunction with the response filed May 23, 2002, Applicants have completely responded to the Request for Information.

Applicants have provided for a four-month extension. No additional extension of time fees, requests for extension of time, petitions, or additional claim fees are believed to be necessary to enter and consider this paper. If, however, any petitions or extensions of time are required or any fees are due in order to enter or consider this paper or enter or consider any paper accompanying this paper, including fees for net addition of claims, applicants hereby request any extensions or petitions necessary and the Commissioner is hereby authorized to charge our Deposit Account #50-1129 for any fees.

Respectfully submitted,
WILEY REIN & FIELDING LLP

Date: January 28, 2003 By: _____
David J. Kulik Reg. No. 36,576

Enclosure: Thimmappaya *et al.* paper

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